

**CLINICAL STUDY PROTOCOL**

**PEGylated rFVIII (BAX 855)**

**A Phase 3b Continuation study of the Safety and Efficacy of PEGylated  
Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in  
Previously Treated Patients with Severe Hemophilia A**

**Short Title: Phase 3b Continuation Study of the Safety and Efficacy of Prophylactic  
BAX 855 in PTPs with Severe Hemophilia A**

**PROTOCOL IDENTIFIER: 261302**

**CLINICAL TRIAL PHASE 3b**

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<b>Study Sponsor(s):</b>	<b>Baxter Healthcare Corporation</b>	<b>Baxter Innovations GmbH</b>
	One Baxter Way	Industriestrasse 67
	Westlake Village, CA 91362	A-1221 Vienna, AUSTRIA

## **1. STUDY PERSONNEL**

### **1.1 Authorized Representative (Signatory) / Responsible Party**

Barbara Valenta-Singer, MD

PPD Global Clinical Development  
Baxter Healthcare Corporation

### **1.2 Study Organization**

The name and contact information of the individuals involved with the study (eg, investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees [ECs], as applicable) will be maintained by the sponsor and provided to the investigator.

## **2. SERIOUS ADVERSE EVENT REPORTING**

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

**ALL SAEs ARE TO BE REPORTED ON THE  
SERIOUS ADVERSE EVENT REPORT (SAER)  
FORM AND REPORTED TO THE SPONSOR  
WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT**

**See SAER form for contact information.  
Further details are also available in the study team roster.**

For definitions and information on the assessment of these events refer to the following:

- AE, Section [12.1](#)
- SAE, Section [12.2](#)
- Assessment of AEs, Section [12.11](#)

### 3. SYNOPSIS

<b>INVESTIGATIONAL PRODUCT</b>	
<b>Name of Investigational Product (IP)</b>	BAX 855
<b>Name(s) of Active Ingredient(s)</b>	PEGylated recombinant factor VIII (PEG-rFVIII)
<b>CLINICAL CONDITION(S)/INDICATION(S)</b>	
<ul style="list-style-type: none"> <li>Previously treated patients (PTPs) with severe hemophilia A (FVIII &lt;1%)</li> </ul>	
<b>PROTOCOL ID</b>	261302
<b>PROTOCOL TITLE</b>	A Phase 3b Continuation study of the Safety and Efficacy of PEGylated Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in Previously Treated Patients with Severe Hemophilia A
<b>Short Title</b>	Phase 3b Continuation Study of the Safety and Efficacy of Prophylactic BAX 855 in PTPs with Severe Hemophilia A
<b>STUDY PHASE</b>	Phase 3b
<b>PLANNED STUDY PERIOD</b>	
<b>Initiation</b>	Anticipated date of enrollment of first subject is September 2013
<b>Primary Completion</b>	December 2016 (100 EDs)
<b>Study Completion</b>	December 2016 (100 EDs)
<b>Duration</b>	The overall duration is approximately 36 months from study initiation to last subject last visit.
<b>STUDY OBJECTIVES AND PURPOSE</b>	
<b>Study Purpose</b>	
To evaluate the safety and efficacy of BAX 855 in a continuation study of prophylaxis of bleeding episodes in PTPs (children and adults, from 0 - 75 years of age) with severe hemophilia A	
<b>Primary Objective</b>	
The co-primary objectives of the study are, 1) To determine the safety of BAX 855 based on incidence of neutralizing inhibitor development and 2) To determine the efficacy of BAX 855 based on ABR as determined by development of spontaneous bleeds (bleeds not associated with trauma).	
<b>Secondary Objective(s)</b>	
<ol style="list-style-type: none"> <li>To determine the total ABR (spontaneous and traumatic bleeds)</li> <li>To determine the rate of success of BAX 855 for treatment of breakthrough bleeding episodes</li> <li>To characterize the success of BAX 855 for treatment of bleeding episodes through the number of BAX 855 infusions needed for the treatment of a bleeding episode and through the length of intervals between bleeding episodes</li> <li>To compare the total weight-adjusted consumption of BAX 855</li> <li>To determine the safety of BAX 855, as assessed by occurrence of AEs and changes in vital signs and clinical laboratory parameters following BAX 855 administration</li> <li>To assess Health-Related Quality of Life (HRQoL) over time for subjects receiving BAX 855</li> </ol>	
<b>Exploratory Objective</b>	
To assess patient satisfaction, patient activity levels, and health resource use over time for subjects receiving BAX 855	

<b>STUDY DESIGN</b>	
<b>Study Type/ Classification/ Discipline</b>	Safety and Efficacy
<b>Control Type</b>	No Control
<b>Study Indication Type</b>	Prevention and Treatment
<b>Intervention model</b>	Parallel
<b>Blinding/Masking</b>	Open-label
<b>Study Design</b>	The study is a Phase 3b prospective, open-label, multicenter study to evaluate the safety and efficacy of BAX 855 prophylaxis in a total of 200 evaluable male PTP subjects with severe hemophilia A from the BAX 855 Ph 2/3 pivotal (Baxter study 261201), surgery (Baxter study 261204), pediatric PTP, other BAX 855 studies, and BAX 855-naïve subjects.
<b>Planned Duration of Subject Participation</b>	All subjects will continue on study until a minimum of 100 EDs per subject have been achieved across all BAX 855 studies in which each subject participated.
<b>Primary Outcome Measure</b>	
Safety: Incidence of neutralizing BAX 855 inhibitor development Efficacy: Spontaneous ABR	
<b>Secondary Outcome Measure(s)</b>	
<p><b>Efficacy</b></p> <ol style="list-style-type: none"> <li>Total ABR (spontaneous and traumatic bleeds)</li> <li>Rate of success of BAX 855 for treatment of breakthrough bleeding episodes</li> <li>Number of BAX 855 infusions needed for the treatment of bleeding episodes</li> <li>Time intervals between bleeding episodes</li> <li>Weight-adjusted consumption of BAX 855</li> </ol> <p><b>Safety</b></p> <ol style="list-style-type: none"> <li>Occurrence of AEs and SAEs</li> <li>Changes in vital signs and clinical laboratory parameters (hematology and clinical chemistry)</li> <li>Immunogenicity                             <ol style="list-style-type: none"> <li>Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG</li> <li>Anti-CHO antibodies</li> </ol> </li> </ol> <p><b>Patient Reported Outcomes (PROs)</b>                      Changes from baseline in the following:</p> <ol style="list-style-type: none"> <li>Bleed and pain severity as measured using the Haemo-SYM questionnaire</li> <li>HRQoL as assessed using the SF-36 questionnaire</li> </ol>	
<b>Exploratory Outcome Measure(s)</b>	
<ol style="list-style-type: none"> <li>Patient satisfaction with treatment will be assessed using the Satisfaction Question Set</li> <li>Patient Activity Level</li> <li>Health resource use data (eg, physician office visits, hospitalizations, length of stay, days missed from work/school)</li> </ol>	

<b>INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION</b>	
<b>Investigational Product(s)</b>	<p><b>BAX 855</b>  <b>Dosage form:</b> injection, powder, lyophilized, for solution</p> <p><b>Dosage frequency:</b> Dose assignment when entering this study will be based on the subject's participation in previous BAX 855 studies, as follows:</p> <ul style="list-style-type: none"> <li>A. On-demand subjects from the Ph2/3 pivotal study with an ABR&gt;0, BAX 855-naïve subjects and subjects joining from the surgery study will receive a fixed dose of BAX 855 45± 5 IU/kg, twice weekly.</li> <li>B. Subjects from the Ph 2/3 pivotal study (excl. on-demand subjects), the pediatric PTP study, or from other BAX 855 studies, with an ABR&gt;0 will be treated with BAX 855 45-80 ± 5 IU/kg twice weekly.</li> <li>C. Subjects from the Ph 2/3 pivotal study (incl. on-demand subjects), the pediatric PTP study, or from other BAX 855 studies, with an ABR=0, will be offered BAX855 30-80 IU/kg q5d.</li> </ul> <p>After each consecutive 6 months of being treated in this study, the dose and/or frequency may be adjusted as follows, depending on the subjects spontaneous ABR estimated at those intervals:</p> <ul style="list-style-type: none"> <li>A. Subjects achieving an ABR&gt;0 on a twice weekly dosing schedule will continue on BAX855 45-80 ± 5 IU/kg twice weekly.</li> <li>B. Subjects achieving an ABR=0 on a twice weekly dosing schedule will be offered BAX855 30-80 IU/kg q5d.</li> <li>C. Subjects achieving an ABR=0 on a q5d dosing schedule will be offered BAX855 30-80 IU/kg q7d.</li> <li>D. Subjects achieving an ABR≤2 on a q5d or a q7d dosing schedule will be offered to stay on their current dosing schedule</li> <li>E. Subjects achieving a 2&lt;ABR≤4 on a q7d dosing schedule will be offered to switch back to BAX855 30-80 IU/kg q5d.</li> <li>F. Subjects achieving an ABR&gt;2 on q5d or ABR&gt;4 on q7d will be switched back to BAX 855 45-80 ± 5 IU/kg twice weekly.</li> </ul> <p><b>Mode of Administration:</b> intravenous bolus</p>
<b>SUBJECT SELECTION</b>	
<b>Targeted Accrual</b>	Approximately 250 PTP male subjects with severe hemophilia A.
<b>Number of Groups/Arms/Cohorts</b>	A single group of BAX 855 prophylaxis
<b>Inclusion Criteria</b>	
<p>Potential Subjects from other BAX 855 studies (Ph 2/3 pivotal, surgery, pediatric PTP, or other BAX 855 studies) will be qualified for the continuation study based on meeting the inclusion criteria and completion of the prior study's End of Study Visit assessments. Any assessments not completed at the End of Study Visit but required as part of screening for the continuation study will be performed at the continuation study Screening Visit. BAX 855 naïve subjects who meet <b>ALL</b> of the following criteria are eligible for this study:</p> <ul style="list-style-type: none"> <li>1. Subject and/or legal representative has/have voluntarily provided signed informed consent.</li> <li>2. Subject is from 0 to 75 years of age at screening.</li> <li>3. Subject is male with severe hemophilia A (FVIII clotting activity &lt; 1%) as confirmed by central laboratory at screening after the appropriate washout period or a documented FVIII clotting activity &lt; 1%.</li> </ul>	

4. Subject has been previously treated with plasma-derived FVIII concentrates or recombinant FVIII for  $\geq 150$  documented previous exposure days (EDs).
5. Subject is currently receiving prophylaxis or on-demand therapy with FVIII.
6. Subject has a Karnofsky (see Section 20.4) or Lansky performance score of  $\geq 60$ .
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count  $\geq 200$  cells/mm<sup>3</sup>, as confirmed by central laboratory at screening.
8. Subject is hepatitis C virus negative (HCV-) by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
9. Subject is willing and able to comply with the requirements of the protocol.

#### **Exclusion Criteria**

Subjects from other BAX 855 studies (Ph 2/3 pivotal, surgery, pediatric PTP, or other BAX 855 studies) will be qualified for the continuation study based on not meeting the study exclusion from that prior study and completion of that study's End of Study Visit assessments. For BAX 855 naïve subjects, those who meet ANY of the following criteria are not eligible for this study:

1. Subject has detectable FVIII inhibitory antibodies ( $\geq 0.4$  BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.
2. Subject has history of FVIII inhibitory antibodies ( $\geq 0.4$  BU using the Nijmegen modification of the Bethesda assay or  $\geq 0.6$  BU using the Bethesda assay) at any time prior to screening.
3. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease).
4. Subject has known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80.
5. Subject has severe chronic hepatic dysfunction [eg,  $\geq 5$  times upper limit of normal alanine aminotransferase (ALT), as confirmed by central laboratory screening, or documented at a local laboratory within 6 months prior to screening, or a documented INR  $> 1.5$ ]
6. Subject has severe renal impairment (serum creatinine  $> 2.0$  mg/dL), as confirmed by central laboratory at screening, or documented at a local laboratory within 6 months prior to screening.
7. Subject has current or recent ( $< 30$  days) use of other PEGylated drugs prior to study participation or scheduled use of such drugs during study participation.
8. Subject has participated in another clinical study involving an investigational product (IP) other than BAX 855 or device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
9. Subject has medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
10. Subject is a family member or employee of the investigator.

<b>STATISTICAL ANALYSIS</b>
<b>Sample Size Calculation</b>
In total, approximately 250 subjects will be enrolled in this study. This sample size is not based on any power calculation for statistical inferences, but on the sample size of BAX 855 studies including the Ph 2/3 pivotal, surgery, pediatric PTP, and other BAX 855 studies as well as EMA guidance on post-marketing investigational studies.
<b>Planned Statistical Analysis</b>
<b>Primary Analysis</b> The number and proportion (Clopper-Pearson exact 95% CI) of subjects who develop inhibitory antibodies to FVIII will be provided. Only the inhibitory antibodies developed after the first exposure to BAX 855 will be included in the analysis.  The primary outcome measure, the Spontaneous ABR, will be assumed to have a negative binomial distribution, the mean ABR (95% CI) will be estimated using a general estimating equation (GEE) model framework (with a logarithmic link function which is the default for the negative binomial distribution), treatment regimen as a fixed effect and subject effect as a random effect, age at baseline as a continuous covariate, and the logarithm of follow-up time (in years) as an offset.
<b>Secondary Analyses</b> <ul style="list-style-type: none"><li>• <b>The total ABR</b> (spontaneous and traumatic bleedings) will be estimated and similarly described as the primary efficacy outcome.</li><li>• Rate of Success of BAX 855 for Treatment of Breakthrough Bleeding Episodes</li></ul> Success will be defined as a rating of excellent or good using the Efficacy Rating Scale for Treatment of Bleeding Episodes, 24 hr after initiation of BAX 855 treatment for the bleed.  Success proportion (95% CI) will be estimated within a general estimating equation (GEE) model framework. The model will account for the fixed effects of bleeding severity, and the random subject effect.  For the dependent variable (success: yes/no) a binomial distribution and a log link will be assumed, and for the subject effect (defined by a repeated statement) an independence correlation structure will be used to start the estimation. Estimated model parameter values and CI limits will then be back-transformed to the original scale by exponentiation. <ul style="list-style-type: none"><li>• <u>Number of BAX 855 Infusions Needed for the Treatment of Bleeding Episodes</u> Frequency tables will be prepared for the number of infusions required for the treatment of a bleed. The median number of infusions (and nonparametric 95% CI) will be estimated.</li><li>• <u>Time Intervals Between Bleeding Episodes</u> The average time interval between 2 consecutive bleeding episodes will be computed for each subject. If a subject does not have any bleeding episode then the observation will be censored at the end of the follow-up time of the respective subject. The median (95% CI) of those average time intervals between 2 bleeding episodes will be estimated.</li><li>• <u>Weight-Adjusted Consumption of BAX 855</u> Consumption of BAX 855 will be summarized as average number of BAX 855 infusions and average weight-adjusted consumption of BAX 855 per month.</li></ul>



- **Haemo-SYM**  
Higher scores on the Haemo-SYM indicate worse symptom severity. Changes from Baseline to End of Treatment in the Haemo-SYM scores will be tested for statistical significance, using a Wilcoxon test for paired samples. Improvement in the Haemo-SYM pain subscale of at least 11 points decreasing will be considered a meaningful improvement (a 1 point change on each pain question). Number and proportion of subjects with meaningful improvement in the Haemo-SYM pain subscale will be tabulated.
- **SF-36**  
Lower scores on SF-36 indicate worse HRQoL. Changes from Baseline to End of Treatment in the SF-36 scores will be tested for statistical significance using a Wilcoxon test for paired samples. Improvement in the SF-36 scale of at least 3 points increasing will be considered a meaningful improvement. The number and proportion of subjects with meaningful improvement in SF-36 will be tabulated.

### **Safety Analysis**

Frequency counts and percentages will be calculated for all treatment arms for SAEs, occurrence of inhibitory and binding antibodies, occurrence of severe allergic reactions, and occurrence of thrombotic events.

AEs that occurred during or after treatment will be presented in summary tables. AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term.

### **Interim Safety Reviews**

The first interim safety review will be done when 35 subjects complete 6 months BAX855 30-80 IU/kg q5d treatment.

Descriptive statistics of ABR of this period will be provided, in addition, the number and percentage (95% CI) of subjects with ABR=0 in this 6 months observed period will be provided.

The second interim safety review will be done when 20 subjects complete 6 months BAX855 30-80 IU/kg q7d treatment.

The analysis of this interim will be similar as interim safety review 1.

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## 5. LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
ABR	annualized bleed rate
AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
AUC(0-∞)	area under the plasma concentration curve from 0 to infinity
BAX 855	product code name for Baxter's PEGylated recombinant FVIII (rFVIII)
BAX 855 naïve Surgery patient	Patients who will come in the continuation study directly from the Surgery study, without being treated before in another BAX 855 study
BU	Bethesda unit
US CFR	US Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CL	total body clearance
Cmax	maximum plasma concentration
(e)CRF	(electronic) case report form
DI	dose intensification
DMC	data monitoring committee
EC	ethics committee
ED	exposure day
ELISA	enzyme-linked immunoabsorbent assay
EMA	European Medicines Agency
FAS	full analysis set
FVIII	factor VIII
GCP	Good Clinical Practice
GEE	general estimating equation
GLM	general linear model

<b>Abbreviation</b>	<b>Definition</b>
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HDL	high density lipoprotein
HIV	human immunodeficiency virus
h	hour(s)
HRQoL	health-related quality of life
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICF	informed consent form
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IP	investigational product
ITI	immune tolerance induction
IU	international unit (s)
INR	international normalized ratio
IR	incremental recovery over time
i.v.	intravenous(ly)
LDL	low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
Mo	Month
MRT	mean residence time
NMC	non-medical complaint
PCR	polymerase chain reaction



<b>Abbreviation</b>	<b>Definition</b>
pdFVIII	plasma-derived factor VIII
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PKFAS	pharmacokinetic full analysis set
PP	per protocol
PRO	patient reported outcomes
PTP	previously treated patient
q5d	Dose every five (5) days
q7d	Dose every seven (7) days
rFVIII	recombinant factor VIII
SAE	serious adverse event
SAER	serious adverse event report
SD	standard deviation
SF-36	Short form-36 questionnaire
SIC	subject identification code
SWFI	sterile water for injection
T1/2	half life
Tmax	time to maximum concentration in plasma
US	United States
VAS	visual analog scale
VLDL	very low density lipoprotein
Vss	volume of distribution at steady state
VWF	von Willebrand factor

## 6. BACKGROUND INFORMATION

### 6.1 Description of Investigational Product

The investigational product (IP) in this study is BAX 855, a PEGylated recombinant full length FVIII (rFVIII), which is intended for use as a FVIII replacement therapy in prophylaxis and treatment of bleeding events in patients with severe hemophilia A.

Today's management of severe hemophilia A includes on-demand treatment for bleeding events and prophylaxis to prevent bleed episodes.<sup>1;2</sup> Current FVIII products have an average half life of 12-14 h,<sup>3;4</sup> thus prophylaxis regimens require infusion of FVIII every other day, or every 2-3 days when based on each patient's individual pharmacokinetic (PK) profile.<sup>5</sup> BAX 855 is designed to maintain normal FVIII activity with extended half life with the intent of maintaining or optimizing efficacy and reduce the frequency of administration.

BAX 855 consists of rFVIII protein molecules (identical to the parent molecule octocog alfa, ADVATE) with covalently bound polyethylene glycol (PEG) chains linked to the protein using a stable linker. The product is reconstituted with sterile water for injection (SWFI) and will be delivered as a solution by bolus infusion. It uses the same stabilizing agents (mannitol, trehalose, histidine, and glutathione) as the rFVIII product (octocog alfa, ADVATE) from which it is derived. PEGylation influences and extends both the *in vivo* half life and the measurable circulating activity of the product (as determined by chromogenic and 1-stage clotting assays). Physicochemical characterization studies have demonstrated that the functional activity of BAX 855 is comparable to that of ADVATE. Additional details can be found in the BAX 855 Investigator Brochure (IB).

As with most FVIII therapy, the IP will be administered intravenously (i.v.) by bolus administration, as individualized prophylaxis or as fixed dose prophylactic treatment and for the treatment of breakthrough bleeding episodes.

The treatment regimens used in this continuation study is based on treatment regimens and treatment outcome from preceding BAX 855 studies. In the BAX 855 Ph 2/3 pivotal study (Baxter study 261201), the pediatric PTP study, the BAX 855 surgery study (Baxter study 261204), and in other BAX 855 studies subjects are on prophylaxis with BAX 855 30 to 80 ± 5 IU/kg every 3 to 4 days. Subjects who have achieved a spontaneous ABR=0 following 6 months of treatment in a previous BAX 855 study will initially be offered BAX 855 30 to 80 ± 5 IU/kg dosing q5d. Subjects who maintain spontaneous ABR=0 after 6 months of BAX 855 dosing q5d will be offered BAX 855 30 to 80 ± 5 IU/kg q7d.

The prophylaxis dose treatment regimens in the present continuation study ( $30$  to  $80 \pm 5$  IU/kg, twice weekly, q5d, or q7d) are developed to assure that subjects have FVIII levels above 1%. The dose and frequency are calculated based on the recorded 1.4 to 1.5 fold extended half life of BAX 855 as compared to ADVATE, as well as FVIII trough level calculations made based on the actual recorded half life and incremental recovery of subjects participating in the phase I study.

The on-demand treatment regimen (doses ranging from  $10$  to  $60 \pm 5$  IU/kg) is based on extensive previous experience from use of ADVATE (additional information can be found in the ADVATE IB). The dosing is further supported by preclinical PK and bleeding model studies as well as the phase I study investigating safety and PK following infusion of  $30$  and  $60$  IU/kg. The FVIII dosing is also aligned with recommendations provided in EMA/CHMP/BPWP/144533/2009.<sup>6</sup> Doses as high as  $60 \pm 5$  IU/kg may be used for the treatment of bleeding episodes based upon experience with these doses with ADVATE.

A minimum of at least 100 exposure days (EDs) in at least 200 subjects was selected based upon the guideline EMA/CHMP/BPWP/144533/2009 for market authorization of FVIII products.<sup>6</sup>

## **6.2 Clinical Condition/Indication**

Hemophilia A is an X-linked recessive, congenital bleeding disorder caused by deficient or defective coagulation FVIII. The absence of FVIII leads to 'spontaneous' bleeding episodes (occurring primarily in joints, muscles, and less commonly, in soft tissues) and to excessive bleeding following trauma or injury. Hemophilia A is currently treated with FVIII replacement using either plasma-derived (pdFVIII) or rFVIII concentrates.<sup>7; 8</sup>

The intended indication for BAX 855 is treatment and prevention of bleeding in subjects with hemophilia A. The study design is in compliance with EMA/CHMP/BPWP/144533/2009 recommendations for the study of FVIII in severe hemophilia A.<sup>6</sup>

## **6.3 Population To Be Studied**

Approximately 250 male PTP subjects with severe hemophilia A, of any ethnic group, ages 0 to 75 years, will be enrolled to achieve a total of 200 evaluable subjects with  $\geq 100$  exposure days (EDs) per subject across all BAX 855 studies in which each subject participates.

Justification for enrollment of adolescent subjects is based on the nonclinical safety requirements outlined in the ICH M3 Guideline, Section 12 as well as the ICH E11 Guideline on clinical investigation of medicinal products in the pediatric population. Hemophilia is a serious and potentially life-threatening disease. Pediatric subjects are expected to benefit from a new recombinant full length FVIII molecule with extended half-life. Moreover, nonclinical repeated toxicology studies, the core safety pharmacology package and the clinical phase 1 study have not raised any safety or tolerability concerns. Furthermore, the parent protein molecule ADVATE has been used extensively in the entire pediatric population with no unforeseen adverse events (see IB of ADVATE). Children < 12 years of age will not be enrolled in the continuation study until enrollment in the BAX 855 pediatric study has been completed. At least 60 evaluable subjects in the BAX 855 continuation study must be < 12 years of age.

#### **6.4 Findings from Nonclinical and Clinical Studies**

BAX 855 is manufactured by covalently binding a PEG reagent with a molecular weight of 20 kDA to Baxter's rFVIII (octocog alfa, ADVATE).

Baxter's octocog alfa is expressed in Chinese Hamster Ovary (CHO) cells by a plasma/albumin free cell culture method and is the active substance in Baxter's licensed product ADVATE. Thus, the viral safety of BAX 855 is ensured by the ADVATE bulk drug substance manufacturing process as any potential risk of contamination with viruses or adventitious agents during the subsequent manufacturing steps of BAX 855 has been minimized. No substances of animal origin are added throughout the entire manufacturing process of BAX 855.

Preclinical studies have demonstrated BAX 855 to have comparable activity and other biochemical properties to ADVATE. The expected prolonged FVIII exposure by BAX 855 was demonstrated in PK studies with a mean residence time (MRT) longer than ADVATE in FVIII knock-out-mice (1.6 fold), rats (1.2 fold) and cynomolgus monkeys (1.5 fold). Prolonged efficacy was shown for BAX 855 in comparison to equivalent doses of ADVATE in two primary pharmacodynamic models in FVIII knock-out mice.

Additional data from nonclinical studies can be found in the BAX 855 IB.

#### 6.4.1 Findings from Clinical Studies

A Phase 1, first-in-human study (Baxter clinical study 261101) to assess the safety and PK of BAX 855 in PTPs age 18 to 65 years of age with severe hemophilia A with  $\geq 150$  EDs to FVIII products was conducted in Europe and Japan. The study investigated safety and PK of single doses of 30 IU/kg and 60 IU/kg BAX 855 compared to the same dose of ADVATE. Subjects were followed for 28 days after BAX 855 administration for safety. Safety assessments included AEs, changes in vital signs, clinical laboratory assessments, and immunogenicity.

A total of 24 subjects were enrolled; 19 were treated and 18 were evaluable for PK analysis. Nine were treated with 30 IU/kg (Cohort 1) and 10 were treated with 60 IU/kg (Cohort 2) of BAX 855, including 2 subjects from Japan.

No subjects developed inhibitors to FVIII or binding antibodies to PEG after BAX 855 infusion. There were no thrombosis-associated events or allergic reactions. No deaths or other SAEs occurred, and none of the 11 non-serious AEs (all mild or moderate) were considered treatment-related. AEs reported following BAX 855 administration included vomiting, nasopharyngitis, upper respiratory tract infection, influenza-like illness, arthralgia, headache, and localized swelling. No significant treatment-related changes in laboratory values or vital signs were recorded. There were no notable differences in the type or rate of AEs experienced by subjects after ADVATE infusion versus BAX 855 infusion.

Eighteen subjects (Cohort 1, n=8; Cohort 2, n=10) were PK evaluable. Based on the one-stage clotting assay, the mean  $T_{1/2}$  (h) was longer for BAX 855 than for ADVATE in both Cohort 1 (13.60 vs 9.90) and Cohort 2 (16.64 vs 11.11). Other PK parameters also supported an improved PK profile for BAX 855 compared to ADVATE.

Based on these data, BAX 855 appears to be safe and well tolerated after single dose administration. The mean  $T_{1/2}$  was 1.4 and 1.5-fold higher for BAX 855 compared to ADVATE (Cohorts 1 and 2, respectively), thereby demonstrating prolonged circulation of BAX 855 compared to ADVATE. These data support the use of the BAX 855 dosing regimens planned in this study.

See BAX 855 IB for periodic updates from other BAX 855 studies.

## **6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects**

Any anticipated risks and benefits associated with administration of BAX 855 are described in the latest issue of the BAX 855 IB.

## **6.6 Compliance Statement**

This study will be conducted in accordance with this protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

## **7. STUDY PURPOSE AND OBJECTIVES**

### **7.1 Study Purpose**

The purpose of the study is to evaluate the safety and efficacy of BAX 855 in a continuation study of the prophylaxis of bleeding episodes in PTP (children and adults, from 0 to 75 years of age) with severe hemophilia A.

### **7.2 Primary Objectives**

The co-primary objectives of the study are:

1. To determine the safety of BAX 855 based on incidence of neutralizing inhibitor development
2. To determine the efficacy of BAX 855 based on ABR as determined by development of spontaneous bleeds (bleeds not associated with trauma).

### **7.3 Secondary Objectives**

#### **7.3.1 Efficacy**

1. To determine the total ABR (spontaneous and traumatic bleeds)
2. To determine the rate of success of BAX 855 for treatment of breakthrough bleeding episodes
3. To characterize the success of BAX 855 for treatment of bleeding episodes through the number of BAX 855 infusions needed for the treatment of a bleeding episode and through the length of intervals between bleeding episodes

4. To compare the total weight-adjusted consumption of BAX 855 for each regimen
5. To assess Health-Related Quality of Life (HRQoL) over time for subjects receiving BAX 855.

### **7.3.2 Safety**

1. To determine the safety of BAX 855, as assessed by occurrence of AEs and changes in vital signs and clinical laboratory parameters following BAX 855 administration
2. To determine the immunogenicity of BAX 855

### **7.4 Exploratory Objectives**

- To assess patient satisfaction, patient activity levels, and health resource use over time for subjects receiving BAX 855

## **8. STUDY DESIGN**

### **8.1 Brief Summary**

This is a Phase 3b, prospective, open label, multi-center study that is a continuation study to evaluate the safety and efficacy of BAX 855 in the prophylaxis of bleeding episodes in 200 evaluable male children and adult PTPs (ages 0 to 75 years) with severe hemophilia A.

### **8.2 Overall Study Design**

This is a Phase 3b, prospective, open label, multi-center study to evaluate the safety and efficacy of BAX 855 in a total of approximately 250 male PTPs (0 to 75 years of age) with severe hemophilia A. Subjects completing BAX 855 studies including the Ph 2/3 pivotal, surgery, pediatric PTP, or other BAX 855 studies, as well as BAX 855-naïve subjects, are candidates for this continuation study. On-demand subjects from the Ph 2/3 pivotal study can enter this continuation study if they are willing to undergo prophylaxis treatment with BAX 855 twice weekly. For subjects entering from a previous BAX 855 study, the BAX 855 dosing schedule will be determined based on their ABR outcome and treatment regimen as follows:

- A. On-demand subjects from the Ph2/3 pivotal study with an ABR>0, BAX 855-naïve subjects and subjects joining from the surgery study will receive a fixed dose of BAX 855  $45 \pm 5$  IU/kg, twice weekly.

- B. Subjects from the Ph 2/3 pivotal study (excl. on-demand subjects), the pediatric PTP study, or from other BAX 855 studies, with an  $ABR > 0$  will be treated with BAX 855  $45-80 \pm 5$  IU/kg twice weekly.
- C. Subjects from the Ph 2/3 pivotal study (incl. on-demand subjects), the pediatric PTP study, or from other BAX 855 studies, with an  $ABR = 0$ , will be offered BAX855 30-80 IU/kg q5d.

After each consecutive 6 months of being treated in this study, the dose and/or frequency may be adjusted as follows, depending on the subjects spontaneous ABR estimated at those intervals:

- A. Subjects achieving an  $ABR > 0$  on a twice weekly dosing schedule will continue on BAX855  $45-80 \pm 5$  IU/kg twice weekly.
- B. Subjects achieving an  $ABR = 0$  on a twice weekly dosing schedule will be offered BAX855 30-80 IU/kg q5d.
- C. Subjects achieving an  $ABR = 0$  on a q5d dosing schedule will be offered BAX855 30-80 IU/kg q7d.
- D. Subjects achieving an  $ABR \leq 2$  on a q5d or a q7d dosing schedule will be offered to stay on their current dosing schedule
- E. Subjects achieving an  $2 < ABR \leq 4$  on a q7d dosing schedule will be offered to switch back to BAX855 30-80 IU/kg q5d.
- F. Subjects achieving an  $ABR > 2$  on q5d or  $ABR > 4$  on q7d will be switched back to BAX 855  $45-80 \pm 5$  IU/kg twice weekly.

The selected dose should be adjusted ( $30-80 \pm 5$  IU/kg) to aim at maintaining a FVIII trough level of at least 1%, as measured quarterly throughout the study.

BAX 855 dosages  $< 45 \pm 5$  IU/kg can only be offered to subjects with a known PK profile of BAX 855 (from BAX 855 Ph2/3, BAX 855 surgery, or other BAX 855 studies). Furthermore, BAX 855 dosages  $< 45 \pm 5$  IU/kg are not permitted in subjects entering the study with  $ABR > 0$ , however if subjects enter the study with an  $ABR = 0$  or develop an  $ABR = 0$  within 6 month treatment with BAX855 twice weekly, dosages  $< 45 \pm 5$  IU/kg are allowable.

Approximately 250 male PTPs will be enrolled to achieve 200 total evaluable subjects. Subjects will continue until completion of a total of at least 100 EDs of BAX 855, at which time they will be given an option to exit or to continue in the study until it is terminated by the sponsor.



The overall study design is illustrated in [Figure 1](#) (Section 20.1).

Subjects transitioning from the other BAX 855 clinical studies mentioned, upon completion of their participation in that study, do not require a washout period prior to blood sampling for screening assessments in the continuation study. Subjects participating in the prior BAX 855 studies can, after signing informed consent, roll over to the continuation study. No more than a 2-week (14 days) administrative break between the End of Study (Study Termination) Visit in the previous BAX 855 study and the Screening Visit for the continuation study is permitted. Subjects with more than a 2-week break must undergo screening assessments for the continuation study. For subjects completing the BAX 855 Phase 2/3 pivotal, surgery, pediatric PTP, or other BAX 855 studies and enrolling in this continuation study, the End of Treatment assessments in that prior study do not need to be repeated (data will be transferred from the previous study). However, if any assessments required at screening in this continuation study were not performed at the End of Treatment Visit from the prior BAX 855 study, then subjects entering this continuation study will complete those assessments at the continuation study Screening Visit. See Section 10.3.1 for more details on Screening Visit assessments.

BAX 855 naïve subjects will undergo a minimum washout period since the last FVIII therapy (on-demand or prophylaxis) of at least 96 hr (aiming to achieve FVIII baseline below 1%), while at the same time beginning screening procedures. Upon completion of the washout period, blood samples will be collected and any other procedures needed to determine eligibility.

BAX 855 will be utilized for the treatment of all breakthrough bleeding episodes. A 4-point Efficacy Rating Scale for Treatment of Bleeding Episodes will be used (see [Table 3](#), Section 8.6.3.1) to assess efficacy of BAX 855. Efficacious treatment will be defined as a response at 24 hours of excellent or good. Rescue therapy with ADVATE may be instituted if an inadequate response to on-demand therapy with BAX 855 is observed.

Subjects who require elective surgery may be enrolled in the BAX 855 Surgery Study if it is open for enrollment. Following an invasive or surgical procedure, subjects may be eligible to return to this continuation study once they are ready to resume their prophylaxis regimen, provided the continuation study is ongoing. These subjects may take an administrative break between the two studies of no more than 2-weeks (14 days) between the surgery End of Study visit and the re-Screening Visit in the continuation study. For subjects returning from the surgery study to the continuation study, the assessments needed to re-enter the continuation study are the same as those included in

the surgery End of Study Visit. Assessments completed in the End of Study Visit for the Surgery study do not have to be repeated in the Continuation study if the break between the studies is not longer than 2 weeks. In addition the inclusion/exclusion criteria should be confirmed. Subjects will be required to maintain electronic diaries (e-diaries) documenting bleeds, treatment administered (BAX 855 and ADVATE), response to treatment with BAX 855 associated with each bleeding episode, untoward events, concomitant medications, non-drug therapies and PROs (see Section 10.3.5). Subjects that exit the continuation study to participate in the surgery study and then return to the continuation study will be re-set to the dosing and infusion schedule corresponding to the beginning of the study and assigned to receive BAX855 45-80 ± 5 IU/kg twice weekly for 6 months.

Following the first dose of BAX 855, subjects will be monitored for safety. Safety assessments will be performed at Screening, at Start of Prophylaxis, at 1 month (± 2 weeks) and every 3 months (± 4 weeks), and End of Study visit, after the subject has started prophylaxis until the subject has completed ≥ 100 EDs of BAX 855 across the Phase 3b continuation study together with other BAX 855 study(ies) in which that subject participated. See Section 20.2, Schedule of Study Procedures and Assessments and Section 20.3, Clinical Laboratory Assessments. Safety assessments include: changes in physical exam, vital signs and clinical laboratory assessments of hematology and chemistry, immunogenicity (inhibitory antibodies for FVIII, binding antibodies for FVIII, BAX 855, PEG, and CHO) and AEs.

### **8.3 Duration of Study Period(s) and Subject Participation**

The overall duration of the clinical study is approximately 36 months from study initiation (i.e., first subject enrolled by signing informed consent) to study completion (ie, last subject last visit). The recruitment period will continue until the last subject has been completed in any preceding BAX 855 study that the sponsor considers to have potential subjects for the continuation study.

The initiation date and the completion date will vary for subjects depending on the BAX 855 studies they participated in and for BAX 855 naïve subjects.

All baseline screening of a subject must be completed no more than 45 days prior to the first infusion of BAX 855 or repeated if more than 45 days have elapsed.

The subject participation period is approximately 6 to 36 months. All subjects will continue on study from enrollment to last study visit until a minimum of BAX 855 100 EDs per subject have been achieved or unless the subject is prematurely discontinued.

Following 100 EDs, subjects will be given the option to exit the study or continue until the entire study is terminated. 100 EDs per subject includes BAX 855 continuation study exposure plus that from any other BAX 855 study(ies) in which the subject has participated.

## **8.4 Outcome Measures**

### **8.4.1 Primary Outcome Measures**

#### **8.4.1.1 Safety**

- Incidence of neutralizing BAX 855 inhibitor development.

#### **8.4.1.2 Efficacy**

- Spontaneous ABR

### **8.4.2 Secondary Outcome Measures**

#### **8.4.2.1 Efficacy**

1. Total ABR (spontaneous and traumatic bleedings).
2. Rate of success of BAX 855 for treatment of breakthrough bleeding episodes
3. Number of BAX 855 infusions needed for the treatment of bleeding episodes
4. Time intervals between bleeding episodes
5. Weight-adjusted consumption of BAX 855

#### **8.4.2.2 Safety**

1. Occurrence of AEs and SAEs
2. Changes in vital signs and clinical laboratory parameters (hematology and clinical chemistry)
3. Immunogenicity
  - a. Binding antibodies (IgG and IgM) to FVIII, BAX 855, and PEG
  - b. Anti-CHO antibodies

#### **8.4.2.3 Patient Reported Outcomes**

Changes from baseline in the following:

1. Bleed and pain severity as measured using the Haemo-SYM questionnaire
2. HRQoL as assessed using the SF-36 questionnaire

### **8.4.3 Exploratory Outcomes Measure**

1. Patient satisfaction with treatment will be assessed using the Satisfaction Question Set
2. Patient Activity Level
3. Health resource use data (eg, physician office visits, hospitalizations, length of stay, days missed from work/school)

### **8.4.4 Randomization and Blinding**

This is a non-randomized, open-label, concurrent, active treatment clinical study.

### **8.5 Study Stopping Rules**

The study will be halted (enrollment and treatment temporarily stopped) or stopped, if the following criterion is met:

- If 2 or more subjects develop anaphylaxis in this continuation study following exposure to BAX 855

The study may be terminated, if one or more of the following criteria are met:

- The sponsor decides to terminate the study based upon its own assessment of safety
- The sponsor decides to terminate the study for administrative reasons

### **8.6 Investigational Product(s)**

#### **8.6.1 Packaging, Labeling, and Storage**

BAX 855 is formulated as a sterile, highly purified protein preparation in lyophilized form for i.v. infusion and is provided in single-dose vials along with a vial of diluent (5 mL SWFI). A butterfly transfer set with luer-lock syringes and a needleless transfer device will be used for reconstitution and bolus i.v. delivery (BAXJECT II highflow (HF) and BAXJECT III, as available). The BAXJECT system is a needleless liquid transfer device with the primary function of transferring diluent from its vial into an evacuated vial containing product requiring reconstitution prior to infusion.

A minimum of 4 lots of BAX 855 manufactured for this study will be used. Four nominal potencies of BAX 855 will be used, depending upon availability: 250, 500, 1,000 and 2,000 IU/vial.

The recommended storage condition for BAX 855 is 2°C to 8°C (36°F to 46°F) and it should not be allowed to freeze. BAX 855 should be stored and protected from light. The

reconstituted product should ideally be used immediately but no longer than 3 h after reconstitution.

For additional information, such as reconstitution instructions, please refer to the BAX 855 IB and/or other specific instructions provided by the sponsor.

For labeling of BAX 855, please refer to the separate document of Master Labels.

### **8.6.2 Administration**

Following reconstitution, BAX 855 should be administered by bolus infusion using plastic syringes provided by the sponsor since proteins such as BAX 855 may adhere to the surface of glass syringes. BAX 855 will be administered i.v., using an appropriately sized syringe, as a bolus infusion over a period of  $\leq 5$  minutes with a maximum infusion rate of 10 mL/min, as described in the BAX 855 IB. The reconstituted BAX 855 must be administered at room temperature and within 3 hours.

### **8.6.3 Description of Treatment**

Subjects can enter the Phase 3b continuation study, either directly via BAX 855 Ph 2/3 pivotal, surgery, pediatric PTP, other BAX 855 studies, or as BAX 855 naïve subjects. Dose assignment when entering this study will be based on the subject's participation in previous BAX 855 studies, as follows:

- A. On-demand subjects from the Ph2/3 pivotal study with an ABR>0, BAX 855-naïve subjects and subjects joining from the surgery study will receive a fixed dose of BAX 855  $45 \pm 5$  IU/kg, twice weekly.
- B. Subjects from the Ph 2/3 pivotal study (excl. on-demand subjects), the pediatric PTP study, or from other BAX 855 studies, with an ABR>0 will be treated with BAX 855  $45-80 \pm 5$  IU/kg twice weekly.
- C. Subjects from the Ph 2/3 pivotal study (incl. on-demand subjects), the pediatric PTP study, or from other BAX 855 studies, with an ABR=0, will be offered BAX855 30-80 IU/kg q5d.

After each consecutive 6 months of being treated in this study, the dose and/or frequency may be adjusted as follows, depending on the subjects spontaneous ABR estimated at those intervals:

- A. Subjects achieving an  $ABR > 0$  on a twice weekly dosing schedule will continue on BAX855  $45-80 \pm 5$  IU/kg twice weekly.
- B. Subjects achieving an  $ABR = 0$  on a twice weekly dosing schedule will be offered BAX855  $30-80$  IU/kg q5d.
- C. Subjects achieving an  $ABR = 0$  on a q5d dosing schedule will be offered BAX855  $30-80$  IU/kg q7d.
- D. Subjects achieving an  $ABR \leq 2$  on a q5d or a q7d dosing schedule will be offered to stay on their current dosing schedule
- E. Subjects achieving an  $2 < ABR \leq 4$  on a q7d dosing schedule will be offered to switch back to BAX855  $30-80$  IU/kg q5d.
- F. Subjects achieving an  $ABR > 2$  on q5d or  $ABR > 4$  on q7d will be switched back to BAX 855  $45-80 \pm 5$  IU/kg twice weekly.

Dose assignment is also illustrated in [Table 1](#) below:

<b>Table 1 BAX 855 Dose and Schedule</b>				
<b>Subjects Entering from Other BAX 855 Studies</b>	<b>0-6 Months</b>	<b>6-12 Months</b>	<b>12-18 Months</b>	<b><math>\geq 18</math> Months</b>
On-demand subjects with $ABR > 0$ from Ph 2/3 pivotal BAX 855 naïve subjects Subjects from surgery study	BAX855 fixed dose $45 \pm 5$ IU/kg twice weekly	$ABR > 0$ : BAX 855 $45-80 \pm 5$ IU/kg twice weekly	$ABR > 0$ : BAX 855 $45-80 \pm 5$ IU/kg twice weekly	$ABR > 0$ : BAX 855 $45-80 \pm 5$ IU/kg twice weekly
		$ABR = 0$ : BAX 855 $30-80 \pm 5$ IU/kg q5d <sup>a</sup>	$ABR > 2$ : BAX 855 $45-80 \pm 5$ IU/kg twice weekly	$ABR > 4$ : BAX 855 $45-80 \pm 5$ IU/kg twice weekly
			$ABR \leq 2$ : BAX 855 $30-80 \pm 5$ IU/kg q5d <sup>a</sup>	
			$ABR = 0$ : BAX 855 $30-80 \pm 5$ IU/kg q7d <sup>a</sup>	
		$2 < ABR \leq 4$ : BAX 855 $30-80 \pm 5$ IU/kg q5d <sup>a</sup>	$ABR \leq 2$ : BAX 855 $30-80 \pm 5$ IU/kg q7d <sup>a</sup>	

<b>Table 1 BAX 855 Dose and Schedule</b>				
<b>Subjects Entering from Other BAX 855 Studies</b>	<b>0-6 Months</b>	<b>6-12 Months</b>	<b>12-18 Months</b>	<b>≥18 Months</b>
Subjects from Ph 2/3 pivotal Subjects from pediatric PTP study Subjects from other BAX 855 studies	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly
	ABR=0: BAX 855 30-80 ±5 IU/kg q5d <sup>a</sup>	ABR>2: BAX 855 45-80 ± 5 IU/kg twice weekly		
		ABR≤2: BAX 855 30-80 ± 5 IU/kg q5d <sup>a</sup>		
		ABR=0: BAX 855 30-80 ± 5 IU/kg q7d <sup>a</sup>	ABR>4: BAX 855 45-80 ± 5 IU/kg twice weekly	
	2<ABR≤4: BAX 855 30-80 ± 5 IU/kg q5d <sup>a</sup>			
		ABR≤2: BAX 855 30-80 ± 5 IU/kg q7d <sup>a</sup>		

<sup>a</sup> Dosing with BAX855 q5d or q7d will be at investigators discretion.

BAX 855 dosages <45 IU/kg can only be offered to subjects with a known PK profile of BAX 855 (from BAX 855 Ph2/3 or BAX 855 PK guided maximum efficacy or BAX 855 surgery).

Furthermore, BAX 855 dosages < 45 ± 5 IU/kg are not permitted in subjects entering the study with ABR>0, however if subjects enter the study with an ABR=0 or develop an ABR=0 within 6 month treatment with BAX855 twice weekly, dosages <45 ± 5 IU/kg are allowable.

For subjects receiving twice weekly prophylaxis and with ABR>2, dosing of BAX 855 may for a 6 month time period target a FVIII trough level of up to a maximum of 10% at investigators discretion and approval by the study medical director.

Subjects meeting either of the following criteria during prophylaxis may have their BAX 855 dose increased and/or frequency of administration increased:

- Two or more spontaneous (not related to trauma) bleeding episodes in the same target joint within any 2-month period, or
- One or more spontaneous (not related to trauma) bleeding episodes in a non-target joint within any 2-month period
- FVIII trough level < 1% and investigator's estimate that study subject has an increased risk of bleeding

Dose adjustment may take place as follows and only after consultation with the study Medical Director and written documentation of the decision which will be recorded in the eCRF:

- The BAX 855 dose regimen may be increased gradually up to a maximum of  $80 \pm 5$  IU/kg and/or the frequency can be changed to twice weekly.

#### **8.6.3.1 Treatment of Bleeding Episodes**

According to the guidelines outlined in [Table 2](#), BAX 855 ( $10-60 \pm 5$  IU/kg) will be used for treatment of bleeding episodes (ie, breakthrough bleeding episodes during prophylaxis). These guidelines may be adjusted by the investigator based upon his or her clinical judgment, and if needed, to allow for dosing below  $10 \pm 5$  IU/kg or above  $60 \pm 5$  IU/kg, based on the severity of the bleed (see [Table 2](#)). The subject or their caregiver, will rate the severity of the bleeding episode as mild, moderate or severe and will rate his overall response for each bleeding episode 24 h ( $\pm 2$  h) after initiating treatment. A 4-point Efficacy Rating Scale for Treatment of Bleeding Episodes ([Table 3](#)) will be used to assess efficacy of BAX 855. Efficacy will not be assessed if ADVATE or any other FVIII product is administered for treatment of bleeding episodes. Efficacy will be defined as a response of good or excellent. As per [Table 3](#), multiple infusions of BAX 855 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded.

When the treatment is controlled, it allows the administration of BAX 855 infusions to maintain hemostasis (FVIII trough levels of 1%) for a maximum of 24 hours after the bleed resolution if required, or the subject can re-start prophylaxis at the previous BAX 855 dose and schedule. Infusions to maintain hemostasis will count as EDs.



<b>Table 2</b> <b>BAX 855 and ADVATE Treatment Guidelines for Bleeding Episodes</b>		
<b>Type of Bleeding Episode</b>	<b>Dose</b>	<b>Frequency of Dosing</b>
<b>Minor</b> Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	10 to 20 ( $\pm 5$ ) IU/kg	Repeat infusions every 12 to 24 h for 1 to 3 days until the bleeding episode is resolved
<b>Moderate</b> Moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma	15 to 30 ( $\pm 5$ ) IU/kg	Repeat infusions every 12 to 24 h for 3 days or more until the pain and moderate disability/incapacity are resolved
<b>Major</b> Significant gastrointestinal bleeding, intracranial, intra-abdominal, or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	30 to 60 ( $\pm 5$ ) IU/kg	Repeat infusions every 8 to 12 h until the bleeding episode is resolved

NOTE: Subjects with life-threatening or gastrointestinal bleeding episodes should be withdrawn from the study.

<b>Table 3</b> <b>Efficacy Rating Scale for Treatment of Bleeding Episodes at 24 <math>\pm</math> 2 Hours from the Initiation of Treatment</b>	
Excellent	Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

### 8.6.3.2 Immune Induction for Inhibitor Development

Subjects who develop a high responder inhibitor ( $> 5$  BU), documented at 2 separate time points within a 2 to 4 week period at a central laboratory, or who develop a confirmed (documented at 2 separate time points within a 2 to 4 week period at a central laboratory)

low responder inhibitor ( $\leq 5$  BU but  $\geq 0.6$  BU) that cannot be adequately managed by the protocol-required prophylactic treatment dosing with BAX 855 will be discontinued from study. The decision to initiate ITI will be made by the subject's physician, and may be discussed with the sponsor's medical director prior to initiation. The regimen used for ITI will be determined by the treating physician but must be approved by the sponsor's Medical Director responsible for this study.

#### **8.6.4 Investigational Product Accountability**

The investigator will ensure that the IP is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP, was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP must be dispensed only at the study site or other suitable location (e.g. infusion center; home, as applicable per study design), as specified in the protocol. Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

#### **8.7 Source Data**

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

## **9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION**

### **9.1 Inclusion Criteria**

Potential subjects from other BAX 855 studies including the Ph 2/3 pivotal, surgery, pediatric PTP, or other BAX 855 studies, will be qualified for the continuation study based on meeting the inclusion criteria and completion of that study's End of Study Visit assessments. Any assessments not completed at the End of Study Visit but required as part of screening for the continuation study will be performed at the continuation study Screening Visit. For the purpose of this study, subjects coming from other BAX 855 studies into the continuation study, will be considered enrolled only after they have completed all procedures and assessments at the End of Study Visit in the previous BAX 855 study.

BAX 855 naïve subjects are eligible to enroll provided they meet **ALL** of the following criteria for this study, and all other BAX 855 studies (except surgery study) are closed to enrollment:

1. Subject and/or legal representative has/have voluntarily provided signed informed consent.
2. Subject is from 0 to 75 years of age at screening.
3. Subject is male with severe hemophilia A (FVIII clotting activity < 1%) as confirmed by central laboratory at screening after the appropriate washout period or a documented FVIII clotting activity <1%.
4. Subject has been previously treated with plasma-derived FVIII concentrates or recombinant FVIII for  $\geq 150$  documented previous exposure days (EDs).
5. Subject is currently receiving prophylaxis or on-demand therapy with FVIII.
6. Subject has a Karnofsky (see Section 20.4) or Lansky performance score of  $\geq 60$ .
7. Subject is human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count  $\geq 200$  cells/mm<sup>3</sup>, as confirmed by central laboratory at screening.
8. Subject is hepatitis C virus negative (HCV-) by antibody or PCR testing (if positive, antibody titer will be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis.
9. Subject is willing and able to comply with the requirements of the protocol.

### **9.2 Exclusion Criteria**

Potential Subjects from other BAX 855 studies including the Ph 2/3 pivotal, surgery, pediatric PTP, or PK-guided maximum efficacy study, will be qualified for the

continuation study based on not meeting the study exclusion from that study and completion of that study's End of Study Visit assessments.

BAX 855 naïve subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Subject has detectable FVIII inhibitory antibodies ( $\geq 0.4$  BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening.
2. Subject has history of FVIII inhibitory antibodies ( $\geq 0.4$  BU using the Nijmegen modification of the Bethesda assay or  $\geq 0.6$  BU using the Bethesda assay) at any time prior to screening.
3. Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease).
4. Subject has known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80.
5. Subject has severe chronic hepatic dysfunction [eg,  $\geq 5$  times upper limit of normal alanine aminotransferase (ALT), as confirmed by central laboratory at screening, or documented at a local laboratory within 6 months prior to screening, or a documented INR  $> 1.5$ ]
6. Subject has severe renal impairment (serum creatinine  $> 2.0$  mg/dL), as confirmed by central laboratory at screening, or documented at a local laboratory within 6 months prior to screening.
7. Subject has current or recent ( $< 30$  days) use of other PEGylated drugs prior to study participation or scheduled use of such drugs during study participation.
8. Subject has participated in another clinical study involving an investigational product (IP) other than BAX 855 or device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
9. Subject has medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.
10. Subject is a family member or employee of the investigator.

### 9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the End of Study Visit (including in cases of withdrawal or discontinuation) are described in Section 10.3.4. The data collected on withdrawn subjects will be used in the analysis and included in the clinical study report.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also may be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The subject develops a confirmed high responder inhibitory antibody to FVIII (> 5 BU by Nijmegen modification of the Bethesda assay) or a low responder inhibitory antibody ( $\leq 5$  BU but  $\geq 0.6$  BU) that cannot be managed by the protocol-required prophylactic or on-demand treatment dosing.
- The subject experiences a severe anaphylactic reaction to BAX 855.
- The subject requires therapy with another PEGylated product (eg, PEG-Interferon).
- The subject frequently misses administration of IP (ie, misses more than 30% of planned prophylactic doses within any 3-month period).
- The subject is non-compliant with study procedures, in the opinion of the investigator.
- The subject repeatedly uses their usual FVIII therapy (in the absence of acceptable justification as accepted by sponsor) for prophylaxis or for treatment of bleeding episodes during the BAX 855 treatment period without an adequate trial (following the BAX 855 treatment guidelines in Table 1) of BAX 855.
- The subject requires a surgical or dental procedure and is not eligible or does not consent for the surgery study, or participates in the surgery study and then refuses to resume participation in this study. If the surgery study is no longer open, the subject will be withdrawn from the continuation study.

- The subject experiences a life-threatening bleeding episode (eg, any gastrointestinal hemorrhage or intracranial hemorrhage).
- The subject experiences severe trauma or emergency surgery requiring extensive FVIII replacement therapy

## **10. STUDY PROCEDURES**

### **10.1 Informed Consent and Enrollment**

Any patient who provides informed consent (ie, signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study.

### **10.2 Subject Identification Code**

The following series of numbers will comprise the SIC: protocol identifier (eg, 261203) to be provided by the sponsor, a 3-digit number study site number (eg, 002) to be provided by the sponsor, and 3-digit subject number (eg, 003) reflecting the order of enrollment (ie, signing the informed consent form). For example, the third subject who signed an informed consent form at study site 002 will be identified as Subject 261203-002003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

### **10.3 Screening and Study Visits**

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the [Figure 1](#). Details on the procedures to be performed at each study visit, including screening, can be found in [Supplement 20.2](#), Schedule of Study Procedures and Assessments, and [Supplement 20.3](#), Clinical Laboratory Assessments.

Study subjects will participate in each of the following study visits with the exception for some subjects as described for the Screening visit.

- Screening visit (exception: this is optional for subjects rolling over from other BAX 855 studies and those who have completed End of Treatment assessments from that other BAX 855 study that match all of those assessments required for the continuation study Screening visit; see Section 10.3.1 for details)
- Start of Prophylaxis
- Follow-up Visits
  - Clinic Visit at 1 month  $\pm$  2 weeks and every 3 months  $\pm$  4 weeks after the start of prophylaxis
- End of Study Visit

### 10.3.1 Screening Visit

The Screening Visit procedures, including laboratory evaluations, are to be completed within 45 days prior to the first infusion of BAX 855, or repeated if more than 45 days have elapsed.

For subjects rolling over from other BAX 855 studies (e.g. Ph 2/3 pivotal, surgery, pediatric PTP), their End of Treatment assessments can satisfy the screening assessments for the BAX 855 Phase 3b continuation study, provided that the same assessments were completed at the End of Treatment visit and no more than 2 weeks (14 days) have elapsed since the End of Treatment visit and the continuation study Screening Visit. If assessments required at the Screening visit in the continuation study were completed at the End of Study Treatment visit for the prior BAX 855 study, they do not have to be repeated at the continuation study Screening visit. However, if the BAX 855 continuation study screening visit requires assessments that were not performed at the End of Study visit for any other BAX 855 study in which subjects participated, then those assessments must be performed at the continuation study Screening Visit.

As a guideline for which assessments need to be performed at this continuation study Screening Visit and which do not for subjects rolling over from another BAX 855 study, Table 4 compares the End of Treatment Assessments from the BAX 855 Ph 2/3 pivotal, surgery, pediatric PTP, and PK-guided maximum efficacy studies, with the Phase 3b Continuation Screening visit.

<b>Table 4</b> <b>Assessments Required at End of Treatment Visit in the BAX 855 Ph 2/3 Pivotal, Surgery, Pediatric PTP, and Other BAX 855 Studies vs. the BAX 855 Phase 3b Continuation Study</b>		
<b>Visit Assessment</b>	<b>BAX 855 Ph 2/3 Pivotal, Surgery, Pediatric PTP, and Other BAX 855 Studies End of Treatment Visit (Completion/Termination) Assessments</b>	<b>BAX 855 Phase 3b Continuation Study Screening Visit Assessments</b>
Informed Consent		X
Eligibility Criteria		X
Medical History <sup>a</sup>		X
Medication History <sup>a</sup>		X
Concomitant Medications <sup>a</sup>	X	X
Non-drug therapies	X	X
Physical exam <sup>a</sup>	X	X
Vital signs <sup>a</sup>	X	X
Adverse Events	X	X
Bleeding Episodes (on study) and their Treatment <sup>f</sup>	X	
Bleeding Episodes and their Treatment <sup>a</sup>	(see footnote a)	X
Hematology <sup>a</sup>	X	X
Clinical Chemistry <sup>a</sup>	X	X
Lipid Panel <sup>a</sup>	X	X
Immunogenicity Assays <sup>b</sup>	X	X
FVIII/VWF assays	X <sup>c</sup>	X <sup>d</sup>
Viral Serology <sup>a</sup>		X
Blood Group <sup>e</sup>		X
Patient e-diary <sup>a</sup>		X

<sup>a</sup> Refer to Section 20.2 and Section 20.3 for more details. Not necessary to repeat these assessments at Screening in this continuation study if Bleeding Episodes (on study; see footnote f below) is completed at End of Study Visit in prior BAX 855 study.

<sup>b</sup> Immunogenicity assessments include: inhibitory antibodies to FVIII, binding antibodies to FVIII, BAX 855 and PEG, and anti-CHO antibodies. Both IgG and IgM binding antibodies are measured.

<sup>c</sup> FVIII/VWF assays include: Factor VIII assays include: 1-stage clotting FVIII activity, FVIII chromogenic activity, and FVIII antigen (and VWF antigen at pre-infusion time points only).

<sup>d</sup> FVIII assays (only) include 1-stage clotting FVIII activity, FVIII chromogenic activity, and FVIII antigen.

<sup>e</sup> Blood group (A, B, AB or O) if historical data not available.

<sup>f</sup> Record of bleeding episodes and their treatment since last study visit in prior BAX 855 study.



For BAX 855 naïve patients, all Screening Assessments will be performed at the Screening Visit, as follows:

- Assessment of inclusion/exclusion criteria
- Clinical Assessments:
  - Medical history
  - Hemophilia history, including,
    - Confirmation of diagnosis and severity
    - Family history of hemophilia
    - Documentation of mutation, if known
    - The presence of any target joints will be documented. A target joint is defined as any single joint (ankles, knees, hips, or elbows) with  $\geq 3$  spontaneous bleeding episodes in any consecutive 6 month period.
  - Bleeding History and Treatment
  - All FVIII replacement therapies used within the last year will be documented, including:
    - FVIII regimen (prophylaxis or on-demand)
    - Product name (or IP name and manufacturer, if applicable)
    - Dose (for prophylaxis, if applicable, and for treatment of bleeding episodes)
    - Frequency of administration (for prophylaxis)
    - Estimate of average number of infusions for each bleeding episode
    - Usual response to treatment for bleeding episodes
    - Assessment of subject's ABR over prior 3-6 months, based on subject's own diary or recall
  - Concomitant medications for last 30 days, and any prior history of use of any PEGylated medication (eg, PEG-interferon) at any time in the past, including treatment indication, date of last administration, and duration of treatment(s), if known
  - Current non-drug therapies
  - Physical exam including height (cm) (for subjects less than 18 years of age at enrollment) and weight (kg)
  - Vital signs (body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg)).

- Laboratory Assessments:  
Following a minimum washout period of 96 h for the BAX 855 naïve subjects, blood will be drawn for the following assessments:
  - FVIII assays:
    - FVIII activity
      - Activated partial thromboplastin-based 1-stage clotting assay
      - Chromogenic assay
    - FVIII antigen
  - Immunogenicity tests:
    - Inhibitory antibodies to FVIII (Nijmegen assay)
    - Binding antibodies (IgG and IgM) to FVIII, BAX 855, PEG
    - Anti-CHO antibodies
  - Hematology, clinical chemistry, and lipid panel
  - Blood group (A, B, AB or O) if historical data not available; if available, historical data will be recorded on the CRF.
  - Viral serology, including:
    - HIV: HIV-1 and HIV-2 Ab
    - HBV: HBsAg, HBsAb, HBcAb
    - HCV: HCvAb
- Diary distribution

Any positive viral serology test will be confirmed at the central laboratory with a new blood sample. HCV titer will be measured by PCR for subjects that are HCV positive.

### 10.3.2 Start of Prophylaxis Visit

The following assessments will be repeated (after Screening) to establish a baseline immediately prior to first prophylactic dose of BAX 855 in this study. The baseline procedures, including laboratory evaluations, are to be completed immediately prior (up to 7 days) to the first infusion of BAX 855:

- Physical examination, including height (for subjects less than 18 years of age at enrollment) and weight and vital signs
- Hematology and chemistry
- Lipid Panel
- Factor VIII assays

- Immunogenicity assays
- Adverse events occurring between screening and start of prophylaxis visit, will be documented
- Concomitant medications
- Non-drug therapies
- All bleeding episodes and their treatment between screening and start of prophylaxis visit will be documented
- Patient Reported Outcomes (PROs; as described in Section 10.3.5)
- Review of subject's diary

### **10.3.3 Follow-up Visits (at month 1 ± 2 Weeks, and Every 3 Months ± 4 Weeks)**

The follow up visits must be scheduled so that blood sampling is done prior to planned dosing of BAX 855 in order for the FVIII measurements to be used as an estimate of FVIII trough level and FVIII peak level 30±15 mins after infusion of BAX855.

The following assessments will be performed at 1 month ± 2 weeks and every 3 months ± 4 weeks after the start of continuation study prophylaxis:

- Physical examination, including height (for subjects less than 18 years of age at enrollment) and weight and vital signs
- Hematology and chemistry
- Lipid panel
- Factor VIII assays
- Immunogenicity assays
- Continuous monitoring for AEs
- Concomitant medications
- Non-drug therapies
- All bleeding episodes and their treatment from first prophylaxis dose of BAX 855 will be documented
- Review of subject's diary
- At each consecutive 6 months visit, the ABR must be estimated and dose regimen may be revised

### **10.3.4 End of Study Visit**

The following assessments will be performed after at least 96 hours washout at the End of Study Visit (approximately 28 days ( $\pm$  2 weeks) after last dose of BAX 855 and at time of early termination, if possible:

- Physical examination including height (for subjects less than 18 years of age at enrollment) and weight and vital signs
- Non-drug therapies
- Hematology, chemistry, lipid panel
- FVIII assays
- Immunogenicity assays
- Continuous monitoring for AEs and concomitant medications
- All bleeding episodes and their treatment from last dose of BAX 855 until study termination will be documented
- PROs (as described in Section [10.3.5](#))
- Review of subject's diary

### **10.3.5 Patient Reported Outcomes (PROs)**

The PRO instruments to be measured in this study are described below. These measures will be administered in this study at 2 time points: Start of Prophylaxis Visit (baseline) and End of Study Visit. Note that due to the unavailability of linguistically validated translations of certain PRO measures in certain countries, some of these questionnaires may not be administered in all countries participating in this study. In addition, subjects who are younger than the minimal age limit required for these assessments will not be required to complete the assessment.

- The following patient reported outcomes will be assessed at Baseline and End of Study Visit:
  - Bleed and pain severity will be measured using the Haemo-SYM for subjects age 18 and older)
  - Health-related quality of life will be assessed using the SF-36 for subjects age 14 and older.
  - Patient satisfaction with treatment will be assessed using the Satisfaction Questionnaire (for subjects age 12 and older, subject completes it themselves; for subjects under age 12, parent completes it on behalf of the subject)
  - Patient Activity Level (for subjects age 12 and older, subject completes it themselves; for subjects under age 12, parent completes it on behalf of the subject)

Details on each of the PROs are described as follows:

- **Haemo-SYM Questionnaire** – This is a self-administered, validated questionnaire designed to assess symptom severity in patients with hemophilia. This measure contains 17 items and includes 2 domains: Bleeds and Pain. Scores for each of these 2 domains can be calculated, with higher scores indicating more severe symptoms. This questionnaire will be administered only to subjects age 18 and older at enrollment)
- **Short Form-36 (SF-36)** – The SF-36 is a self-administered, validated questionnaire designed to measure generic HRQoL. This 36-item questionnaire measures 8 domains, including: Physical functioning, Role-physical, Bodily pain, General health, Vitality, Social functioning, Role emotional, and Mental health. Two summary scores can be calculated, the Physical Component Score, and the Mental Component Score. Additionally, scores can be calculated for each of the 8 domains. Higher scores indicate better health status. This questionnaire will be administered only to subjects age 14 and older at enrollment.
- **Patient Satisfaction Questionnaire** – This questionnaire is a non-validated measure that assesses the subject's (or via their caregiver) level of satisfaction with their treatment. For BAX 855 naïve subjects and BAX 855 naïve surgery subjects, at the End of Study Visit, the questionnaire also assesses the subject's preference between his previous treatment prior to the study and BAX 855. This questionnaire will be administered to all age groups. For subjects age 12 and older at enrollment, the subject completes it themselves and for subjects under age 12 at enrollment, a parent completes it on behalf of the subject.
- **Patient Activity Level** – Subjects will also be asked to estimate their activity levels. This will consist of a few questions asking subjects (or their caregiver) to rate their current level of activity. These data will be collected for all age groups. For subjects age 12 and older at enrollment, the subject completes it themselves and for subjects under age 12 at enrollment, a parent completes it on behalf of the subject.

In addition, the following will be collected where applicable, for each occurrence:

- **Health Resource Use** – The subject (or their caregiver) will record the following events: days missed from work/school (as appropriate) and days not able to perform normal activities outside of work/school due to hemophilia, physician office visits, hemophilia treatment site visits, emergency room visits (reason and number), hospitalizations (reason, dates of hospitalization and associated length of stay). These data will be collected for all age groups.

#### **10.4 Medications and Non-Drug Therapies**

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

- Medications:
  - Any PEGylated medication (eg, PEG-interferon)
  - Any investigational drug, biologic, or device
  - Any FVIII other than BAX 855 or ADVATE (during the course of the study)

A subject who has taken any of these medications or received any of these non-drug therapies will be considered a protocol deviation.

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
  - ADVATE, provided by the study site, is permitted for:
    - o Treatment of bleeding episodes and prophylaxis following enrollment until first prophylactic dose of BAX 855
    - o During the observation period between the last Follow-up Visit and End of Study Visit
    - o Rescue therapy for bleeding episodes that do not respond to BAX 855 during the study
    - o Any ADVATE taken, regardless of whether it is provided by the study site or not, will be documented.
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding during the study

- Any medications deemed necessary by the subject's physician to treat or prevent any medical condition
- Any over-the-counter medication used by the subject to treat symptoms or signs
- Supplemental vitamins, minerals
- Non-drug therapies:
  - Any non-drug therapy (eg, physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

### **10.5 Subject Diary**

A subject diary will be provided to each subject at the Screening Visit to record the following information:

1. Infusion record for BAX 855
2. Infusion record for ADVATE
3. Details of bleeding episodes and response to treatment
4. Untoward events
5. Concomitant medications (including immunizations) and non-drug therapies
6. PROs

Subjects and/or their legally authorized representatives will be trained on use of the diary during the screening visit. Diaries will be provided in electronic form and remain with the subject for the duration of the study.

Subject entries in the diary serve as source records. During the study, the investigator has access to the database holding the subject diary data. Upon retrieval of subject diaries at site closure, the site will receive the pdf files with the subject entries, including the audit trail. The data will be transmitted to the eCRF by a validated transfer process. Any eCRFs changes are to be documented in an audit trail.

The investigator will review the diary for completeness and request missing information periodically (at the latest at each subject visit) and in a timely manner. Untoward events recorded in the diary will be documented as AEs in the eCRF according to the investigator's discretion and clinical judgment.

## 10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Subjects have the option to exit the study once they have 100 EDs with BAX 855. If a subject opts not to exit the study once they have completed 100 EDs, they can continue the study until an additional 50 EDs, or at such time that the Sponsor deems the BAX 855 study complete.

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, adverse event (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, progressive disease, non-compliance with IP/protocol violation(s)), study terminated by sponsor, or other (reason to be specified by the investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded in the appropriate eCRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3, Clinical Laboratory Assessments.

All unused IP provided to the subject will be returned to the study site.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the



details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

### **10.7 Procedures for Monitoring Subject Compliance**

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures, other than subjects' diaries, will be used to monitor subject compliance.

Subject compliance with the BAX 855 prophylaxis regimens will be monitored by review of subject diaries.

## **11. ASSESSMENT OF EFFICACY**

### **11.1 Annualized Bleed Rate (ABR)**

The primary measure of efficacy is the annualized bleed rate (ABR). The bleed rate will be assessed based upon each individual bleed, spontaneous or traumatic, recorded in the subject's diary, and/or recorded in the physician/nurse/clinic notes. A bleed is defined as subjective (eg, pain consistent with a joint bleed) or objective evidence of bleeding which may or may not require treatment with FVIII. Bleeds occurring at the same anatomical location (eg, right knee) with the same etiology (eg, spontaneous vs. injury) within 24 h of onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (eg, knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

### **11.2 Rate of Success of BAX 855 for Treatment of Bleeding Episodes**

The key secondary measure of efficacy is the rate of success of BAX 855 to treat bleeding episodes. Success will be determined by the subject or subject's caregiver. If the bleeding episode is managed in the clinic/hospital, the efficacy rating may be performed by the investigator. BAX 855 efficacy will be evaluated for each bleeding episode and will be assessed 24 h ( $\pm$  2 h) after initiating treatment using the Efficacy Rating Scale for Treatment of Bleeding Episodes (Table 5). Success is defined as a response of Excellent or Good at the 24-h post-infusion time point. Response to BAX 855 will be recorded in the subjects' diaries and/or clinic/hospital notes.

<b>Table 5</b> <b>Efficacy Rating Scale for Treatment of Bleeding Episodes</b>	
Excellent	Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

### **11.3 Number of BAX 855 Infusions Needed for the Treatment of Bleeding Episodes**

The number of BAX 855 infusions needed for each bleeding episode is determined by the subject, his caregiver, and/or clinician treating the subject, and is based upon the subject's response to treatment, using the Efficacy Rating Scale for Treatment of Bleeding Episodes in [Table 3](#). An infusion is defined as completion of administration of the calculated dose of BAX 855. If an infusion is interrupted, eg, due to vascular access issues, and must be re-started, it will be recorded as 1 infusion. If an infusion is terminated for any reason prior to completion of infusion and not restarted, it will be recorded as an infusion; reasons for interruption of the infusion will be recorded.

### **11.4 Time Intervals Between Bleeding Episodes**

The time interval between bleeding episodes will be calculated based upon the date and time reported for each bleeding episode. The subject, his caregiver, and/or clinician will determine when a bleeding episode has occurred (see [Section 11.1](#) above). The time interval will be defined as the date/time from when a recent bleed is stopped to the start day/time of the next bleed.

### **11.5 Weight-Adjusted Consumption of BAX 855**

Weight-adjusted consumption of BAX 855 will be determined based upon the record in subjects' diaries of amount of BAX 855 infused and the subject's weight, as measured in the clinic.

## 12. ASSESSMENT OF SAFETY

### 12.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

### 12.2 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV). Seroconversion to HBV is only considered an SAE in the absence of vaccination; seroconversion of HBsAb from negative to positive will not be considered an SAE (or an AE).
  - Development of a confirmed inhibitor to FVIII with an inhibitor level  $\geq 0.6$  BU, as measured by Nijmegen assay
  - Severe hypersensitivity/allergic reactions to BAX 855

### 12.3 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from Baxter. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxter) will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

### 12.4 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

### 12.5 Severity

Subjects rolling over from a prior BAX 855 study who experienced an AE that has not been resolved, will have any ongoing AEs and changes in severity of AEs, documented as part of the safety data for the BAX 855 continuation study.

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.

- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

## 12.6 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE assessed as not related or unlikely related, the investigator shall provide an alternative etiology. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not related to the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)

- Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
  - Reappearance of a similar reaction upon re-administration (positive rechallenge)
  - Positive results in a drug sensitivity test (skin test, etc.)
  - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
- Another etiology is unlikely or significantly less likely

These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

### **12.7 Preexisting Diseases**

For subjects rolling over into the Continuation study from a prior BAX 855 study, AEs having occurred in one of these other BAX 855 studies and which are still ongoing in this Continuation study will be considered as “ongoing” and not as a preexisting disease.

Preexisting diseases that are present before entry in to the study are described in the medical history, and that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, frequency, or duration of a preexisting disease, the event must be described on the AE CRF.

### **12.8 Unexpected Adverse Events**

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, IB, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

For the purposes of this study, each unexpected AE experienced by a subject undergoing study-related procedures will be recorded on the AE CRF.

### **12.9 Untoward Medical Occurrences Not Considered Adverse Events**

For all subjects, each **serious** untoward medical occurrence experienced before the first IP exposure (eg, from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAE Report and on the AE CRF. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before the first IP exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

For the purposes of this study, each of the following non-serious events experienced after the first IP exposure will not be considered an AE, and thus, not included in the analysis of AEs:

- Hospital or clinic visits for administration of BAX 855
- Hospitalization for routine bleeding episode management that could be managed in the clinic or home-setting but for which the subject was hospitalized
- Hospitalizations for planned medical or surgical procedures, eg, placement of a central venous line
- Hospitalization or prolongation of hospitalization intended only for social reasons.
- Hospital admittance without in-patient hospitalization or emergency room visit/admittance in itself (although the event triggering the visit may be an SAE).
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period
- Bleeding episodes/hemophilia-related events

Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy. If a bleeding episode was caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (eg, abrasion of skin). Therefore, any BAX 855 related bleeding event (epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding) will not be reported as AEs. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.

### 12.10 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE**. NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg reconstitution difficulty
- Missing components
- Damage to the product or unit carton

- A mislabeled product (potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product will be returned to the sponsor for inspection and analysis according to procedures.

### **12.11 Assessment of Adverse Events**

For subjects entering from other BAX 855 studies, any ongoing AEs from prior BAX 855 studies will be documented until study completion/discontinuation in this continuation study.

For the purposes of this study and for all subjects, each non-serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before the first IP exposure will be recorded on the AE CRF; these events are considered to be untoward medical occurrences and will not be considered as AEs and will not be included in the analysis of AEs.

For BAX 855 naïve subjects, each AE from the first IP exposure until study completion/discontinuation date will be recorded on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.4). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.5
- Severity as defined in Section 12.8
- Causal relationship to IP exposure as defined in Section 12.9

If the severity rating for an ongoing AE changes before the event resolves, the AE will not be reported a second time, instead the original AE report will be revised. For purposes of data capture the highest severity rating during the course of a single AE will be the severity rating entered on the AE CRF.

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF.



Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first.

Subjects rolling over from a prior BAX 855 study who experienced an AE that has not been resolved, will have any ongoing AEs documented as part of the safety data for this BAX 855 continuation study.

AEs that were resolved in the previous BAX 855 studies will be documented as medical history for subjects who enter this Ph 3b continuation study. If a subject exited the study to participate in the surgery trial, upon return AEs that started and resolved during the surgery study will be documented as (interim) medical history.

Deviations from the protocol-specified dosage (including overdosing, underdosing, abuse, and withdrawal), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness; no additional reporting on CRFs is necessary.

### **12.12 Medical, Medication, and Non-Drug Therapy History**

At screening, the subject's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 12.8). Medical history including surgery will include the following body systems, along with start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; genitourinary; metabolic; infectious disease; and psychiatric.

All medications taken and non-drug therapies received from 30 days before enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

Any prior use of any PEGylated medication (name of drug, indication, and dates of use), at any time in the past, will be recorded on the CRF.

### **12.13 Physical Examinations**

At screening and subsequent study visits (as described in Section 20.2), a physical examination will be performed on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.10), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

### **12.14 Clinical Laboratory Parameters**

All assessments will be performed at a central laboratory, according to the laboratory manual. Blood samples that remain after study testing is done may be stored and used for additional testing. Samples will be destroyed after a maximum of 2 years from the time the final study report has been completed.

#### **12.14.1 Hematology, Clinical Chemistry, and Lipid Panel**

The hematology panel will consist of complete blood count [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), and leukocytes (ie, white blood cell count)] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils, as a percentage of total white blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), CD4 counts (at screening only) and platelet counts.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

The lipid panel will consist of cholesterol, very low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides.

Blood will be obtained for assessment of hematology, clinical chemistry and lipid parameters at Screening, Start of Prophylaxis Visit, Follow-up Visits at 1 month and every 3 months, and End of Study Visit. Hematology, clinical chemistry and lipid assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at the central laboratory.

### **12.14.2 Blood Type**

For subjects who do not have documentation of their blood type in their medical record, blood ABO blood type will be determined.

### **12.14.3 FVIII Activity and Antigen**

Factor VIII activity will be measured using the one-stage clotting assay and the chromogenic assay. FVIII antigen will be measured using an ELISA assay. Blood will be obtained for the FVIII assessments at Screening, Start of Prophylaxis Visit, Follow-up Visits at 1 month and every 3 months from the start of prophylaxis, and End of Study Visit.

### **12.14.4 Immunogenicity Assays**

The primary study and safety assessment is the immunogenicity of BAX 855 which will be assessed by measurement of the following antibodies:

- Inhibitory antibodies to FVIII – measured by the Nijmegen modification of the Bethesda assay
- Binding antibodies to FVIII, BAX 855, and PEG. Both IgG and IgM antibodies will be measured using an ELISA assay.
- Anti-CHO antibodies

A low titer (responder) inhibitor is defined as  $\leq 5$  BU but  $\geq 0.4$  BU. A high titer (responder) inhibitor is defined as  $> 5$  BU by Nijmegen modification of the Bethesda assay. Inhibitors must be documented at 2 separate time points within a 2 to 4 week period at a central laboratory.

Inhibitory antibodies to FVIII will be measured using the Nijmegen modification of the Bethesda inhibitor assay.

Binding antibodies to FVIII and BAX 855, as well as to PEG, will be measured using ELISA. Both IgG and IgM binding antibodies for FVIII, BAX 855, and PEG will be routinely tested. Based on the variability of these tests, only samples with titers  $\geq 1:80$  can be confirmed and will be evaluated as positive. Furthermore, only increases of more than 2 titer steps between pre- and post-treatment samples will be considered positive for treatment-related antibody development. IgG subclass 1-4, IgA (using ELISA) and IgE antibodies (using ImmunoCaps, Phadia) may be assessed as clinically indicated.

The assay for antibodies to CHO protein will use CHO protein derived from cultures of untransfected cells. Testing for binding of anti-CHO protein antibodies will be performed

on citrate-anti-coagulated plasma using an ELISA employing polyclonal anti-human IgG antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

Blood will be obtained for these assessments at Screening, Start of Prophylaxis Visit, Follow-up Visits at 1 month and every 3 months, and End of Study Visit.

#### **12.14.5 Viral Serology**

Viral serology testing will include HIV-1 and HIV-2 antibody, HBsAb, HBsAg, HBcAb, and HCV Ab. HCV or HIV titer will be confirmed by PCR for all subjects reported as HCV or HIV positive. All assessments will be performed at Screening only. Any positive test will be repeated using a new blood sample.

#### **12.14.6 Assessment of Laboratory Values**

##### **12.14.6.1 Assessment of Abnormal Laboratory Values**

The investigator's assessment of each abnormal standard clinical laboratory value (ie, hematology, clinical chemistry and lipids) is to be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.4 and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.7), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie because it was due to a preexisting disease (described in Section 12.7), due to a lab error, due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) shall be re-tested.

#### **12.14.7 Biobanking**

Backup samples of citrated plasma and serum should be taken and stored appropriately for additional analysis, if necessary. These samples may be used for re-testing, tests required per regulatory guidelines, further evaluation of an AE, or follow-up of other test results.

Blood samples that remain after study testing is done may be stored and used for additional testing (eg, further evaluation of an abnormal test or an AE). Samples will be stored in a coded form for a maximum of 2 years after the final study report has been completed and subsequently will be destroyed.

### **12.15 Vital Signs**

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (for subjects less than 18 years of age at the time of enrollment)(in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured at Screening, a Start of Prophylaxis Visit, at Follow-up Visits at 1 month and every 3 months, and at End of Study Visit.

Blood pressure will be measured when subjects are in the sitting position.

Vital sign values are to be recorded on the CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1 and record the medical diagnosis (preferably), symptom, or sign, on the AE CRF). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE CRF. If the abnormal value was not deemed an AE, the investigator will indicate the reason on the source record, ie because it was due to an error, due to a preexisting disease (described in Section 12.7), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

## **13. STATISTICS**

### **13.1 Sample Size and Power Calculations**

In total, approximately 250 subjects will be enrolled in this study. This sample size is not based on any power calculation for statistical inferences, but on the sample size of BAX 855 studies including the phase 2/3 pivotal, surgery, pediatric PTP, and other BAX 855 studies as well as EMA guidance on post-marketing investigation studies.

## **13.2 Datasets and Analysis Cohorts**

### **13.2.1 Safety Analysis Set**

The Safety Analysis Set will comprise all subjects treated with at least 1 BAX 855 dose. All safety analyses will be performed on the Safety Analysis Set.

### **13.2.2 Full Analysis Set**

The Full analysis set will be the same as the safety analysis set. All efficacy analyses will be performed on the Full Analysis Set.

### **13.2.3 Per Protocol Analysis Set**

The Per Protocol Analysis Set (PP) will comprise all subjects from Full analysis set who have no major deviations from the protocol affecting the study results. Major protocol deviations are defined in the Protocol Deviation Plan.

In case a subject needs dose adjustment, as a most conservative approach, the last dose of the respective subject will be taken into account in the analysis.

## **13.3 Handling of Missing, Unused, and Spurious Data**

Missing data will not be imputed.

## **13.4 Methods of Analysis**

### **13.4.1 Primary Outcome Measure**

#### **13.4.1.1 Primary Safety Outcome Measure**

The number and proportion (Clopper-Pearson exact 95% CI) of subjects who develop inhibitory antibodies to FVIII will be provided. Only the inhibitory antibodies developed after the first exposure to BAX 855 will be included in the analysis, the inhibitory antibodies developed before the first exposure to Bax 855 will be listed separately.

#### **13.4.1.2 Primary Efficacy Outcome Measure**

The primary outcome measure, the Spontaneous ABR, will be assumed to have a negative binomial distribution, mean ABR (95% CI) will be estimated using a general estimating equation (GEE) model framework (with a logarithmic link function which is the default for the negative binomial distribution), treatment regimen as a fixed effect and subject effect as a random effect, age at baseline as a continuous covariate, and the logarithm of follow-up time (in years) as an offset.

## **13.4.2 Secondary Outcome Measures**

### **13.4.2.1 Total ABR**

The mean total ABR (spontaneous and traumatic bleedings) (95% CI) will be estimated and described similarly as the primary efficacy outcome, using a general estimating equation (GEE) model with subject effect as a random effect, age at baseline as a continuous covariate, and the logarithm of follow-up time (in years) as an offset.

### **13.4.2.2 Rate of Success of BAX 855 for Treatment of Breakthrough Bleeding Episodes**

Success will be defined as a rating of excellent or good using the Efficacy Rating Scale for Treatment of Bleeding Episodes, 24 hr after initiation of BAX 855 treatment for the bleed.

Success proportion (95% CI) will be estimated within a general estimating equation (GEE) model framework pooled. The model will account for the fixed effects, bleeding severity, age at baseline as a continuous covariate, and the random subject effect.

For the dependent variable (success: yes/no) a binomial distribution and a log link will be assumed, and for the subject effect (defined by a repeated statement) an independence correlation structure will be used to start the estimation. Estimated model parameter values and CI limits will then be back-transformed to the original scale by exponentiation.

### **13.4.2.3 Number of BAX 855 Infusions Needed for the Treatment of Bleeding Episodes**

Frequency tables will be prepared for the number of infusions required for the treatment of a bleed. The median number of infusions (and nonparametric 95% CI) will be estimated.

### **13.4.2.4 Time Intervals Between Bleeding Episodes**

The average time interval between 2 consecutive bleeding episodes will be computed for each subject. If a subject does not have any bleeding episode then the observation will be censored at the end of the follow-up time of the respective subject. The median (95% CI) of those average time intervals between 2 bleeding episodes will be estimated.

### **13.4.2.5 Weight-Adjusted Consumption of BAX 855**

Weight-Adjusted Consumption of BAX 855 for prophylaxis, treating bleeding episodes and in total per subject will be summarized separately as average number of BAX 855

infusions and average weight-adjusted consumption of BAX 855 per month. Only the bleeding episodes consumption with BAX 855 will be summarized.

### **13.4.3 Patient Reported Outcomes**

#### **13.4.3.1 Haemo-SYM**

Higher scores on the Haemo-SYM indicate worse symptom severity. Changes from Baseline to End of Treatment in the Haemo-SYM scores will be tested for statistical significance using a Wilcoxon test for paired samples. Improvement in the Haemo-SYM pain subscale of at least 11 points decreasing will be considered a meaningful improvement (a 1 point change on each pain question). Number and proportion of subjects with meaningful improvement in the Haemo-SYM pain subscale will be tabulated.

#### **13.4.3.2 SF-36**

Lower scores on SF-36 indicate worse HRQoL. Changes from Baseline to End of Treatment in the SF-36 scores will be tested for statistical significance, using a Wilcoxon test for paired samples. Improvement in the SF-36 scale of at least 3 points increasing will be considered a meaningful improvement. Number and proportion of subjects with meaningful improvement in the SF-36 will be tabulated.

### **13.4.4 Safety Analysis**

Frequency counts and percentages will be calculated for SAEs, occurrence of inhibitory and binding antibodies, occurrence of severe allergic reactions, and occurrence of thrombotic events.

AEs that occurred during or after treatment will be presented in summary tables. AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term.

Vital signs and clinical laboratory parameters at the Start of Prophylaxis Visit, the follow-up visit at 1 month and every 3 months, and the End of Study Visit will be descriptively summarized.

### **13.4.5 Exploratory Outcome Measures**

The exploratory outcome measures will be descriptively summarized and listed.



### **13.5 Planned Interim Safety Review of the Study**

Two (2) interim safety reviews are planned for this study. The results of the safety reviews will not impact the study design and sample size.

#### **13.5.1 Interim Safety Review 1**

This interim safety review will be done when 35 subjects complete 6 months BAX855 30-80 IU/kg q5d treatment.

Descriptive statistics of ABR of this period will be provided, in addition, the number and percentage (95% CI) of subjects with ABR=0 in this 6 months observed period will be provided.

#### **13.5.2 Interim Safety Review 2**

This interim safety review will be done when 20 subjects who complete 6 months BAX855 30-80 IU/kg q7d treatment.

The analysis of this interim will be similar as interim safety review 1.

### **14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

### **15. QUALITY CONTROL AND QUALITY ASSURANCE**

#### **15.1 Investigator's Responsibility**

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other

authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

#### **15.1.1 Investigator Report and Final Clinical Study Report**

The investigator will submit a written report of the study's status to the sponsor, as described in the Clinical Study Agreement.

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

#### **15.2 Training**

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

#### **15.3 Monitoring**

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

#### **15.4 Auditing**

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

#### **15.5 Non-Compliance with the Protocol**

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the

sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxter) will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

### **15.6 Laboratory and Reader Standardization**

Not applicable; a central laboratory/reader will be used for all clinical assessments.

## **16. ETHICS**

### **16.1 Subject Privacy**

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

### **16.2 Ethics Committee and Regulatory Authorities**

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

### **16.3 Informed Consent**

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable regulatory requirements and

ICH GCP. An assent form may be provided and should be signed by patients less than 18 years of age. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study (see Section 16.3).

#### **16.4 Data Monitoring Committee**

This study will not require a Data Monitoring Committee (DMC) for routine or ad hoc safety reviews.

### **17. DATA HANDLING AND RECORD KEEPING**

#### **17.1 Confidentiality Policy**

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

#### **17.2 Study Documentation and Case Report Forms**

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (Section 8.7), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and

initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

### **17.3 Document and Data Retention**

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

## **18. FINANCING AND INSURANCE**

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

## **19. PUBLICATION POLICY**

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

**20. SUPPLEMENTS**

**20.1 Study Flow Chart**

**Figure 1**  
**Study Design for Baxter Clinical Study 261302**  
**BAX 855 Continuation Study**

<b>BAX 855 Dose and Schedule</b>				
<b>Subjects Entering from Other BAX 855 Studies</b>	<b>0-6 Months</b>	<b>6-12 Months</b>	<b>12-18 Months</b>	<b>≥18 Months</b>
On-demand subjects with ABR>0 from Ph 2/3 pivotal BAX 855 naïve subjects Subjects from surgery study	BAX855 fixed dose 45 ± 5 IU/kg twice weekly	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly
		ABR=0: BAX 855 30-80 ± 5 IU/kg q5d <sup>a</sup>	ABR>2: BAX 855 45-80 ± 5 IU/kg twice weekly	ABR>4: BAX 855 45-80 ± 5 IU/kg twice weekly
			ABR≤2: BAX 855 30-80 ± 5 IU/kg q5d <sup>a</sup>	
			ABR=0: BAX 855 30-80 ± 5 IU/kg q7d <sup>a</sup>	
		2<ABR≤4: BAX 855 30-80 ± 5 IU/kg q5d <sup>a</sup>	ABR≤2: BAX 855 30-80 ± 5 IU/kg q7d <sup>a</sup>	
Subjects from Ph 2/3 pivotal Subjects from pediatric PTP study Subjects from other BAX 855 studies	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly  ABR=0: BAX 855 30-80 ± 5 IU/kg q5d <sup>a</sup>	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly	ABR>0: BAX 855 45-80 ± 5 IU/kg twice weekly
		ABR>2: BAX 855 45-80 ± 5 IU/kg twice weekly	ABR≤2: BAX 855 30-80 ± 5 IU/kg q5d <sup>a</sup>	
		ABR>4: BAX 855 45-80 ± 5 IU/kg twice weekly	2<ABR≤4: BAX 855 30-80 ± 5 IU/kg q5d <sup>a</sup>	
		ABR≤2: BAX 855 30-80 ± 5 IU/kg q7d <sup>a</sup>		

<sup>a</sup> Dosing with BAX855 q5d or q7d will be at investigators discretion.

**20.2 Schedule of Study Procedures and Assessments**

Procedures/Assessments	Screening Visit <sup>l</sup>	Study Visits		End of Study Visit <sup>a</sup> (28 d ± 2 Wks After Last Dose)
		Start of Prophylaxis (Up to 7 Days Prior to First Prophylaxis)	Follow-Up Visit at 1 Mo (1 Mo ± 2 Wks & Every 3 Mo ± 4 Wks)	
Informed Consent <sup>b</sup>	X			
Eligibility Criteria	X			
Medical History <sup>c</sup>	X			
Medication History <sup>d</sup>	X			
Concomitant Medications <sup>e</sup>	X	X	X	X
Non-drug Therapies	X	X	X	X
Physical Exam <sup>f</sup>	X	X	X	X
Adverse Events	X <sup>m</sup>	X	X	X
Laboratories <sup>g</sup>	X	X	X	X
Vital Signs <sup>h</sup>	X	X	X	X
Bleeding episodes and their Treatment <sup>i</sup>	X	X	X	X
PROs <sup>j</sup>		X		X
Patient e-diary <sup>k</sup>	X	X	X	X
IP Treatment		X	X	
ABR Estimation <sup>n</sup>			X	

<sup>a</sup> Includes for cases of withdrawal or discontinuation.

<sup>b</sup> Occurs at enrollment (prior to any study-specific procedure).

<sup>c</sup> Medical history to include hemophilia history.

<sup>d</sup> Medication history to include documentation of all FVIII replacement therapies used within the last year.

<sup>e</sup> Concomitant medications in the last 30 days and any prior history of use of any PEGylated medication (eg, PEG-interferon) at any time in the past.

*Continued on Next Page*

*Continued*

- <sup>f</sup> Physical exam to include a measurement of height (cm) (for subjects less than 18 years of age at enrollment) and weight (kg).
- <sup>g</sup> For laboratory assessments, see Section 20.3.
- <sup>h</sup> Vital signs to include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg).
- <sup>i</sup> Indicates that adverse events, medications, non-drug therapies, and bleeding episodes and their treatment will be continuously monitored and specifically measured at these time points.
- <sup>j</sup> PROs to include the following depending on patient age: bleed and pain severity using Haemo-SYM (age 18 and older), health-related quality of life using SF-36 (age 14 and older), patient satisfaction with treatment using the Satisfaction Questionnaire, and Patient Activity Level.
- <sup>k</sup> E-diaries are to include patient documentation of bleeds, treatment administered and response to BAX 855, and other data as detailed in Section 10.5.
- <sup>l</sup> The screening visit procedures, including laboratory evaluations, are to be completed within 45 days prior to the first infusion of BAX 855. Screening procedures for BAX naïve subjects include: confirmation of diagnosis & severity; family history of hemophilia; documentation of a mutation, if known; presence of any target joints; all FVIII replacement therapies used within the last year (see Section 10.3.1 for additional details).
- <sup>m</sup> For subjects rolling over from a prior BAX 855 study into this continuation study.
- <sup>n</sup> At each consecutive 6 months visit.



### 20.3 Clinical Laboratory Assessments

Assessments	Screening Visit	Study Visits		End of Study Visit <sup>a</sup> (28 d ± 2 Wks After Last Dose)
		Start of Prophylaxis (Up to 7 Days Prior to First Prophylaxis)	Follow-Up Visit at 1 Mo (1 Mo ± 2 Wks & Every 3 Mo ± 4 Wks)	
<b>Hematology</b>				
Hemoglobin	X (W)	X (W)	X (W)	X (W)
Hematocrit	X (W)	X (W)	X (W)	X (W)
Red blood cell count	X (W)	X (W)	X (W)	X (W)
White blood cell count with differential <sup>b</sup>	X (W)	X (W)	X (W)	X (W)
Mean corpuscular volume (MCV)	X (W)	X (W)	X (W)	X (W)
Mean corpuscular hemoglobin concentration (MCHC)	X (W)	X (W)	X (W)	X (W)
Platelet count	X (W)	X (W)	X (W)	X (W)
CD4 count	X (W)			
<b>Clinical Chemistry</b>				
Sodium	X (S)	X (S)	X (S)	X (S)
Potassium	X (S)	X (S)	X (S)	X (S)
Chloride	X (S)	X (S)	X (S)	X (S)
Bicarbonate	X (S)	X (S)	X (S)	X (S)
Total protein	X (S)	X (S)	X (S)	X (S)
Albumin	X (S)	X (S)	X (S)	X (S)
Alanine aminotransferase (ALT)	X (S)	X(S)	X (S)	X (S)
Aspartate aminotransferase (AST)	X (S)	X (S)	X (S)	X (S)
Total bilirubin	X (S)	X (S)	X (S)	X (S)
Alkaline phosphatase	X (S)	X (S)	X (S)	X (S)
Blood urea nitrogen (BUN)	X (S)	X (S)	X (S)	X (S)
Creatinine	X (S)	X (S)	X (S)	X (S)
Glucose	X (S)	X (S)	X (S)	X (S)
Lipid panel <sup>c</sup>	X (S)	X (S)	X (S)	X (S)

Assessments	Screening Visit	Study Visits		End of Study Visit <sup>a</sup> (28 d ± 2 Wks After Last Dose)
		Start of Prophylaxis (Up to 7 Days Prior to First Prophylaxis)	Follow-Up Visit at 1 Mo (1 Mo ± 2 Wks & Every 3 Mo ± 4 Wks)	
Viral serology <sup>d</sup>				
HIV-1Ab	X (S)			
HIV-2 Ab	X (S)			
HBcAb	X (S)			
HBsAb	X (S)			
HBsAg	X (S)			
HCVAb	X (S)			
Specialty Tests				
Blood type <sup>c</sup>	X (W)			
FVIII Tests				
1-stage clotting FVIII activity	X (P)	X (P)	X (P)	X (P)
FVIII chromogenic activity	X (P)	X (P)	X (P)	X (P)
FVIII antigen	X (P)	X (P)	X (P)	X (P)
Immunogenicity Assays <sup>f</sup>				
Inhibitory Abs to FVIII	X (P)	X (P)	X (P)	X (P)
Binding Abs to FVIII, BAX 855 and PEG	X (P)	X (P)	X (P)	X (P)
Anti-CHO Abs	X (P)	X (P)	X (P)	X (P)

Abbreviations: W= whole blood; P= plasma; S= serum.

<sup>a</sup> Includes for cases of withdrawal or discontinuation.

<sup>b</sup> White blood cell count to include basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

<sup>c</sup> Lipid panel to include cholesterol, VLDL, LDL, HDL, and triglycerides.

<sup>d</sup> For viral serology, any positive viral antibody test will be repeated using a new blood sample. Any HCV positive sample will be tested by PCR for viral titer.

<sup>e</sup> If historical data on blood group type is available, this may be recorded in the CRF and blood type does not need to be measured.

<sup>f</sup> For inhibitory antibodies, both IgG and IgM antibodies will be measured.

### 20.4 Karnofsky Score

<b>Karnofsky Score for Performance Status</b>	
<b>Score</b>	<b>Definition</b>
100	Normal, no complaints; no evidence of disease
90	Able to perform normal activity; minor signs or symptoms of disease
80	Able to perform normal activity with effort; some signs or symptoms of disease
70	Cares for self, unable to perform normal activity or to do active work
60	Requires occasional assistance but is able to care for most of own needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated, although death not imminent
20	Very sick; hospitalization necessary; active supportive treatment required
10	Moribund; Fatal processes progressing rapidly
0	Dead

Source: Karnofsky et al.<sup>9</sup>

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**INVESTIGATOR ACKNOWLEDGEMENT**

**PEGylated rFVIII (BAX 855)**

**A Phase 3b Continuation study of the Safety and Efficacy of PEGylated  
Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in  
Previously Treated Patients with Severe Hemophilia A**

**PROTOCOL IDENTIFIER: 261302**

**CLINICAL TRIAL PHASE: PHASE 3B**

**ORIGINAL: 2013 JUN 18**

**OTHER PROTOCOL ID(s)**

**NCT Number: TBD**

**EudraCT Number: 2013-002236-24**

**IND NUMBER: 15299**

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

---

Signature of Coordinating Investigator

Date

---

Print Name and Title of Coordinating Investigator

---

Signature of Sponsor Representative

Date

Barbara Valenta-Singer, MD

PPD Global Clinical Development